Phase IIa study of dabigatran etexilate in children with venous thrombosis: pharmacokinetics, safety, and tolerability

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Abstract: Essentials Dabigatran etexilate may provide a new treatment option for pediatric venous thromboembolism. Children aged 1 to < 12 years were given dabigatran etexilate in an open-label, single-arm study. The pharmacokinetic-pharmacodynamic relationship was similar to that seen in adult patients. There were no serious adverse events, bleeding events or recurrent venous thromboembolism. SUMMARY: Background The current standard-of-care treatments for pediatric venous thromboembolism (VTE) have limitations. Dabigatran etexilate (DE), a direct thrombin inhibitor, may offer an alternative therapeutic option. Objectives To assess the pharmacokinetics, pharmacodynamics, safety, and tolerability of a DE oral liquid formulation (OLF) in pediatric patients with VTE. Patients/Methods Patients who had completed planned treatment with low molecular weight heparin or oral anticoagulants for VTE were enrolled in two age groups (2 to < 12 years and 1 to < 2 years), and received a DE OLF based on an age-adjusted and weight-adjusted nomogram. Originally, patients were to receive a DE OLF twice daily for 3 days, but the protocol was amended to a single dose on day 1. The primary endpoints were pharmacokinetics/pharmacodynamics-related: plasma concentrations of DE and its metabolites; activated partial thromboplastin time (APTT), ecarin clotting time (ECT), and dilute thrombin time (dTT); and pharmacokinetic (PK)-pharmacodynamic (PD) correlation. Safety endpoints included incidence rates of bleeding events and all other adverse events (AEs). Results Eighteen patients entered the study and received the DE OLF (an exposure equivalent to a dose of 150 mg twice daily in adults). The projected steady-state dabigatran trough concentrations were largely comparable between pediatric patients and adults. The PK/PD relationship was linear for ECT and dTT, and non-linear for APTT. No serious or severe AEs, bleeding events, or recurrent VTEs were reported. Mild AEs were reported in three patients in the single-dose group (screening period) and in one patient in the multiple-dose group (on-treatment period). Conclusion The current study supports the further evaluation of DE OLFs in pediatric patients with VTE.

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ORIGINAL ARTICLE

Phase IIa study of dabigatran etexilate in children with venous thrombosis: pharmacokinetics, safety, and tolerability

J. M. L. HALTON,* M. ALBISETTI,† B. BISS,‡ L. BOMGAARS,§ M. BRUECKMANN,¶** S. GROPPER,¶ R. HARPER,†† F. HUANG,‡‡ M. LUCIANI,§§ H. MAAS,¶¶ I. TARTAKOVSKY¶ and L. G. MITCHELL***

**Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario, Canada; †Hematology Department, University Children's Hospital, Zürich, Switzerland; ‡Clinical Development, Boehringer Ingelheim RCV, Vienna, Austria; §Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA; ¶Clinical Development and Medical Affairs, Boehringer Ingelheim Pharma, Ingelheim; **Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany; ††Clinical Operations, Boehringer Ingelheim, Bracknell, UK; ‡‡Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA; §§OncoHematology Department, Bambino Gesù Children's Hospital, Rome, Italy; ¶¶Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharma, Biberach, Germany; and ***University of Alberta, Edmonton, Alberta, Canada*

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Essentials

- Dabigatran etexilate may provide a new treatment option for pediatric venous thromboembolism.
- Children aged 1 to < 12 years were given dabigatran etexilate in an open-label, single-arm study.
- The pharmacokinetic–pharmacodynamic relationship was similar to that seen in adult patients.
- There were no serious adverse events, bleeding events or recurrent venous thromboembolism.

Summary. *Background:* The current standard-of-care treatments for pediatric venous thromboembolism (VTE) have limitations. Dabigatran etexilate (DE), a direct thrombin inhibitor, may offer an alternative therapeutic option. *Objectives:* To assess the pharmacokinetics, pharmacodynamics, safety, and tolerability of a DE oral liquid formulation (OLF) in pediatric patients with VTE. *Patients/Methods:* Patients who had completed planned treatment with low molecular weight heparin or oral anticoagulants for VTE were enrolled in two age groups (2 to < 12 years and 1 to < 2 years), and received a DE OLF based on an age-adjusted and weight-adjusted nomogram. Originally, patients were to receive a DE OLF twice daily for 3 days, but the protocol was amended to a single dose on day 1. The primary endpoints were pharmacokinetics/pharmacodynamics-related: plasma concentrations of DE and its metabolites; activated partial thromboplastin time (APTT), ecarin clotting time (ECT), and dilute thrombin time (dTT); and pharmacokinetic (PK)–pharmacodynamic (PD) correlation. Safety endpoints included incidence rates of bleeding events and all other adverse events (AEs). *Results:* Eighteen patients entered the study and received the DE OLF (an exposure equivalent to a dose of 150 mg twice daily in adults). The projected steady-state dabigatran trough concentrations were largely comparable between pediatric patients and adults. The PK/PD relationship was linear for ECT and dTT, and non-linear for APTT. No serious or severe AEs, bleeding events, or recurrent VTEs were reported. Mild AEs were reported in three patients in the single-dose group (screening period) and in one patient in the multiple-dose group (on-treatment period). *Conclusion:* The current study supports the further evaluation of DE OLFs in pediatric patients with VTE.

Keywords: anticoagulants; dabigatran; direct thrombin inhibitors; pediatrics; venous thromboembolism.

Correspondence: Jacqueline M. L. Halton, Children's Hospital of Eastern Ontario, University of Ottawa, 401 Smyth Road, Ottawa, ON K1H 8L1, Canada
Tel.: +1 613 737 7600 (ext. 2370)
E-mail: halton@cheo.on.ca

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Introduction

The prevalence of venous thromboembolism (VTE) in children is approximately 0.07–0.14 events per 10 000 children, and has increased in recent years [1–3]. The current standard of care for VTE in pediatric patients is unfractionated heparin (UFH) or low molecular weight heparin (LMWH) followed by LMWH, or treatment with

a vitamin K antagonist (VKA) [4–6]. However, each of these treatment options has limitations: UFH and LMWH require parenteral administration, and may lead to heparin-induced thrombocytopenia and osteopenia; and VKA has a narrow therapeutic index, requires frequent International Normalized Ratio (INR) monitoring, and is associated with multiple food and drug interactions [4,6]. The direct thrombin inhibitor dabigatran, which is orally administered as the prodrug dabigatran etexilate (DE), warrants consideration as an alternative agent, as it has been shown to be effective for the treatment of VTE in adults, and may overcome some of the limitations associated with current treatments [7–9].

The treatments currently recommended for children with VTE are based on extrapolation of data obtained from trials in adults. There are significant differences in the etiology of VTE between adults and children, but, once VTE has occurred, the types of treatment required follow a similar management approach. However, there are differences between adults and children in terms of developmental physiology and pharmacology; therefore, trials to evaluate the pharmacokinetics, pharmacodynamics, and safety of DE in children are required [5,10].

Dabigatran is predominantly excreted via the urine [11], so dosing according to renal function may lead to comparable exposure between adults and pediatric patients [12]. To date, the data on dabigatran in pediatric plasma *in vitro* and in pediatric patients are similar to those seen in adults (e.g. pharmacokinetics and the relationship between pharmacokinetics and pharmacodynamics in children; and safety results in adolescent patients) [13,14]. The planned pediatric clinical trial program for DE has adopted a comprehensive and considered stepwise approach to safety, in order to minimize potential exposure in this vulnerable patient group. First, the safety and tolerability of DE were confirmed in adolescents aged 12–18 years [14], and its use was subsequently evaluated in younger children aged 2–12 years and 1–2 years, and finally in infants and neonates (aged 0 to < 1 year) [15].

Objective

The objective of the current study was to assess pharmacokinetic (PK) and pharmacodynamic (PD) data, and to evaluate the preliminary tolerability and safety of an oral liquid formulation (OLF) of DE in pediatric patients with VTE aged 2 to < 12 years and 1 to < 2 years.

Methods

This was an open-label, multinational, multicenter, nonrandomized, uncontrolled, single-arm study. The target population comprised patients (male or female) aged between 1 year and < 12 years, with an objective diagnosis of VTE, who had completed planned treatment with LMWH or the oral anticoagulant VKA for VTE. The end of planned treatment was defined as no further need for anticoagulant therapy. Patients should have been off standard therapy for long enough for the INR and activated partial thromboplastin time (APTT) to be within normal limits. Full inclusion and exclusion criteria are shown in Table 1.

According to the initial protocol, at least eight patients would be enrolled in each age group. However, the sample size in the younger age group was amended to at least four patients, in agreement with the Paediatric Committee of the European Medicines Agency (EMA) in the European Paediatric Investigation Plan. The sample size was not based on a power calculation, as eight patients per age group is generally considered to be sufficient for exploratory evaluations, including an assessment of whether the observed pharmacokinetics are sufficiently described by the model-predicted pharmacokinetics. The sample size could have been extended if this was deemed to be necessary.

All patients in the study received the DE OLF for a minimum of 5 days after and within 1 month of the last dose of standard therapy; there was no control group. Originally, patients were to receive weight-adjusted doses of DE twice daily for 3 days. However, following protocol amendment, patients were to receive a single dose on day 1. This change was in line with EMA and US Food and Drug Administration guidance, which states that, for drugs with linear pharmacokinetics in adults, single-dose studies in the pediatric population often allow sufficient PK assessment [16]. Single dosing also minimized patient exposure to study medication. Under the amended protocol, single doses were calculated by use of a nomogram based on Hayton's formula, which scales adult doses down according to a child's expected renal function, based on their weight and age [12]; age-adjusted and weight-adjusted doses were estimated to yield an exposure equivalent to a dose of 150 mg twice daily in adult patients. In the multiple-dose group, patients were dosed according to a weight-based dosing method only.

A dose conversion factor of 0.646 was applied to the calculated capsule dose to correct for dosing with the OLF. The conversion factor was based on results from a relative bioavailability study (NCT02171611), which showed that a single dose of the OLF resulted in 55% higher exposure than that obtained with capsules. There was a 30-day follow-up. Assessments made during the study are shown in Table S1.

The study was conducted in accordance with the Declaration of Helsinki [17] and International Conference on Harmonisation Good Clinical Practice guidelines [18], following approval by institutional review boards/independent ethics committees of participating centers and the competent authority.

Data monitoring committee

Safety and tolerability were monitored by an independent data monitoring committee (DMC), which was composed

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Male or female aged 1 to < 12 years
Objective diagnosis of VTE
End of planned treatment with LMWH or the oral anticoagulant VKA for VTE. Patients should have been off standard therapy for long enough for the INR and APTT to be within normal limits. Study medication should be given within 1 month of the last dose of standard therapy
Written informed consent from parent or legal guardian and agreement from patient (if applicable)
Exclusion criteria
Weight < 9 kg
Conditions associated with an increased risk of bleeding:
History of hemorrhagic stroke
Major surgery within 4 weeks of visit 2 (the dosing visit)
Any planned procedure that might put the patient at an increased risk of bleeding within 5 days of taking study medication
History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding
Gastrointestinal hemorrhage within the year prior to screening unless the cause has been permanently eliminated, e.g. with surgery
History of gastroduodenal ulcer disease
History of hemorrhagic disorder or bleeding diathesis
Required concurrent treatment with another LMWH, UFH, oral anticoagulant or antiplatelet agent
Fibrinolytic agents within 48 h of DE administration
Uncontrolled hypertension on antihypertensive medication (systolic and/or diastolic BP above the upper limit of normal for age and sustained over 24 h)
Renal dysfunction (eGFR of < 80 mL min^{-1} 1.73 m^{-2}) or requirement for dialysis
Active infective endocarditis
Hepatic disease:
Active liver disease, including known hepatitis A, B, or C
Persistent ALT, AST or alkaline phosphate level of > 2 × ULN
Women who have reached menarche with a positive pregnancy test result or who are not using a medically accepted contraceptive method
Anemia (hemoglobin level of < 80 g L^{-1}) or thrombocytopenia (platelet count of < 80 × 10^9 L^{-1}) at screening
Patients who have taken prohibited or restricted medication within a week of the first dose of study medication other than prior VTE treatment
Patients who have received an investigational drug in the last 30 days prior to screening
Patients allergic/sensitive to any component of the study medication
Patients considered to be to unreliable to participate in the trial/any condition that would not allow safe participation in the trial in the opinion of the investigator

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BP, blood pressure; eGFR, estimated glomerular filtration rate; INR, International Normalized Ratio; LMWH, low molecular weight heparin; UFH, unfractionated heparin; ULN, upper limit of normal; VKA, vitamin K antagonist; VTE, venous thromboembolism.

of three independent members (all experts in the field of pediatric hematology). The DMC reviewed data on an ongoing basis after every three patients and after the last patient in each group had completed treatment. Patients were enrolled in two age groups: 2 to < 12 years and 1 to < 2 years, sequentially. Recruitment to the younger group commenced following the DMC assessment of safety data from the older age group. On the basis of the monitored safety data, the DMC advised on whether the trial should continue as planned, be modified, or be discontinued.

Study endpoints

As specified in the Statistical Analysis Plan, the primary analyses of PK/PD endpoints were limited to the single-dose cohort; descriptive PK/PD data from the multiple-dose cohort are reported.

PK endpoints The primary PK endpoints were the plasma concentrations of total and free dabigatran, unchanged DE, and the intermediate metabolites BIBR 951 BS and BIBR 1087 SE. The planned times for PK sample collection were 1, 2, 4, 6, and 10 h postdose in the single-dose group. To determine the similarity with adult data, geometric mean (gMean) concentrations at 10 h after a single dose of DE in the pediatric patients were extrapolated to steady-state trough conditions. In order to project the steady-state dabigatran plasma concentration, an accumulation ratio was calculated on the basis of the dosing interval and the assumed terminal half-life ($t_{1/2}$).

PD endpoints The primary PD endpoints were central measurements of APTT, ecarin clotting time (ECT) and dilute thrombin time (dTT) at 2 h and 10 h after intake of study medication. The PK–PD relationship was evaluated by the use of total dabigatran concentrations and the PD values APTT, ECT, and dTT (including the values of predose samples).

Safety endpoints Preliminary safety data for the DE OLF were collected. The primary safety endpoints of the study were the incidence of all bleeding events (major, minor, and clinically relevant non-major) [19] and the incidence of all adverse events (AEs). AEs were classified

according to screening, on-treatment, post-treatment and post-study periods. AEs that occurred before intake of study medication were assigned to screening. The on-treatment period included AEs that occurred after the first dose until 3 days after the last treatment in the multiple-dosing group, and AEs that occurred during 48 h after study medication in the single-dose group; the on-treatment period also included AEs that began before treatment but worsened in intensity during treatment. AEs that occurred after the on-treatment period, up until (and including) visit 3 (follow-up period, which was scheduled 30 days [± 7 days] after intake of study medication) were assigned to the post-treatment period; the post-study period began after visit 3.

Secondary safety endpoints were changes in laboratory and clinical parameters, and global assessment of the tolerability of study medication, which was provided by the investigator using a five-point scale (good, satisfactory, not satisfactory, bad, or not assessable) immediately after the patient had taken the study medication. As part of the global assessment of tolerability, patients who were old enough were asked to assess the taste of the study medication (very good, good, satisfactory, bad, or very bad) and describe the taste itself (bitter, sweet, salty, sour, or other). Other endpoints included the occurrence of clinical outcomes, including recurrent thrombosis, post-thrombotic syndrome, pulmonary embolism, and total and VTE-related mortality.

Bioanalytic methods

Concentrations of total dabigatran, free dabigatran, DE, and intermediate metabolites were analyzed with validated HPLC–tandem mass spectrometry methods at Nuvisan GmbH, Neu-Ulm, Germany [14]. Analysis of APTT, ECT and dTT was performed at Menal GmbH, Emmendingen, Germany. Clotting times were determined with an MC 10 PLUS coagulometer (ABW Medizin und Technik, Lemgo, Germany) [14]. The coefficient of variation (CV), which is a measure of assay imprecision, was ≤ 6.1% for all coagulation parameters.

Samples were thawed at ≈ 37 °C in a waterbath, centrifuged for 3 min at 1000 × *g*, and mixed well before the coagulation assays were performed.

dTT The plasma sample was diluted 1 : 8 with 0.9% isotonic sodium chloride solution. Fifty microliters of the diluted study sample and then 100 μL of R1 (normal pooled plasma) were pipetted into a cuvette, and the mixture was incubated for 2 min at 37°C, before 100 μL of R2 (human calcium thrombin) was added; the time lag between the addition of R2 and clot formation determined the dTT.

APTT Fifty microliters of study sample and 50 μL of kaolin/cephalin reagent were pipetted into a cuvette, and incubated for 3 min at 37 °C, after which 50 μL of 0.025 M $CaCl_2$ was added; the time lag between the addition of $CaCl_2$ and clot formation determined the APTT.

ECT Seventy-five microliters of study sample and then 75 μL of imidazole/veronal buffer (one part imidazole buffer plus 0.77 parts veronal buffer) were pipetted into a cuvette. The mixture was incubated for 2 min at 37 °C, and then 75 μL of ecarin (6 IU mL^{-1}) was added; the time lag between the addition of ecarin and clot formation determined the ECT.

Data analysis

Descriptive statistical methods were applied to safety, PK, PD and clinical endpoints. For PK endpoints, the maximum concentration (C_{max}), time from dosing to the maximum concentration (t_{max}) and area under the concentration–time curve from time interval 0 up to the last quantifiable data point (AUC_{0-tz}) were calculated and presented as gMean and geometric CV (gCV), or median and range. A linear regression model and a non-linear maximum effect model were used for analysis of the PK–PD relationship. The safety analysis was based on all patients who received at least one dose of the DE OLF. The PK, PD and PK/PD analysis included all treated patients who provided at least one PK/PD observation and had no relevant protocol violations.

Results

A total of 20 pediatric patients were enrolled (Fig. 1). However, one patient did not have an objective diagnosis at screening, and a second patient had hepatic disease reported at visit 2. Therefore, 18 patients entered the study, which was conducted at seven active centers in six countries. All participants completed the planned observation time; there were no discontinuations. Three patients received multiple doses of the DE OLF (twice daily for 3 days). Six patients aged 1 to < 2 years and nine patients aged 2 to < 12 years were treated with a single dose of the DE OLF.

There were more male than female patients (61% versus 39%). The mean ages were 17.3 months (standard deviation [SD] 4.0 months) in the group aged 1 to < 2 years, and 5.2 years (SD 2.6 years) in the single-dose group aged 2 to < 12 years. Additional baseline characteristics are shown in Table 2; those for the three patients who received multiple doses before the protocol was amended are shown in Table S2. All 18 patients were included in the treated and PK sets.

PK results

Patients aged 1 to < 2 years In the single-dose group of patients aged 1 to < 2 years, the results for total

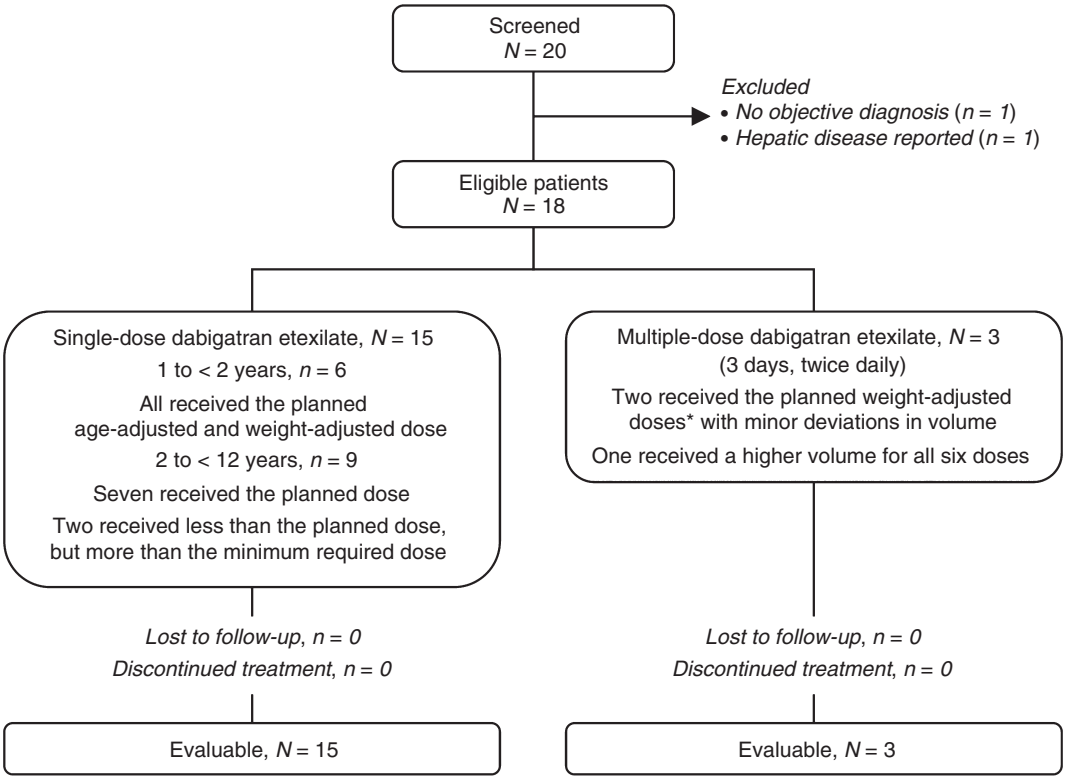

Fig. 1. Patient flow through the study.

dabigatran plasma concentration were as follows: gMean C_{max}, 129 ng mL^{-1}; concentration 10 h postdose (C_{10}), 34.8 ng mL^{-1}; and AUC_{0-tz}, 715 ng mL^{-1} h^{-1}. The gCVs were 9.84%, 41.4%, and 22.5%, respectively (Table 3; Fig. 2). Free dabigatran concentrations were approximately 10–15% lower than total dabigatran concentrations (Table S3).

Patients aged 2 to < 12 years In the single-dose group of patients aged 2 to < 12 years, gMean C_{max}, C_{10} and AUC_{0-tz} were 116 ng mL^{-1}, 28.2 ng mL^{-1}, and 658 ng mL^{-1} h^{-1}, respectively, for total dabigatran plasma concentration, with gCVs of 38.6%, 37%, and 32.5% (Table 3; Fig. 2). Free dabigatran PK parameters are shown in Table S3. The projected steady-state dabigatran trough concentrations in the current study were largely comparable to those seen in adult patients in the RE-COVER trial; that is, they fell between the first and third quartiles of the adult RE-COVER concentrations (Table 4) [7].

PK results for the three patients who received multiple doses of the DE OLF are shown in Table S4.

In all treated patients, plasma concentrations of unchanged dabigatran and the intermediate metabolites were low or undetectable.

PD results

For both single-dosing age groups, the mean coagulation times for APTT, dTT and ECT were prolonged at 2 h postdose and then fell towards baseline values at 10 h (Table 5). Owing to a very limited amount of evaluable data from the multiple-dose group, PD data were not included in the PD analysis.

PK–PD relationship

For the single-dose group, linear PK–PD relationships were observed for dTT and ECT, as shown by R values close to 1 and slope parameters that were significantly different from zero (Fig. 3B, C). For ECT (1 to < 2 years), ECT (2 to < 12 years), dTT (1 to < 2 years), and dTT (2 to < 12 years), slope and R^2 estimates, respectively, were: 0.322 s mL ng^{-1} (standard error [SE] 0.015 s mL ng^{-1}) with R^2 = 0.970; 0.298 s mL ng^{-1} (SE 0.039 s mL ng^{-1}) with R^2 = 0.764; 0.113 s mL ng^{-1} (SE 0.008 s mL ng^{-1}) with R^2 = 0.919; and 0.164 s mL ng^{-1} (SE 0.013 s mL ng^{-1}) with R^2 = 0.859. As the PK–PD relationship for APTT is known to be non-linear in adults, non-linear regression lines were fitted to the concentration–APTT data (Fig. 3A). Other than the baseline parameter,

Table 2 Baseline characteristics of patients in the single-dose groups

	Single dose	
	1 to < 2 years	2 to < 12 years
Treated patients, *N* (%)	6 (100)	9 (100)
Female, *n* (%)	2 (33)	3 (33)
Race, *n* (%)		
White	5 (83)	6 (67)
Asian	1 (17)	3 (33)
Age (years), mean (SD)	1.4 (0.3)	5.2 (2.6)
Minimum	1	2
Maximum	2	8
Height (cm), mean (SD)	80.0 (6.8)	110.9 (17.3)
Weight (kg), mean (SD)	10.68 (2.27)	22.56 (11.00)
BMI (kg m^{-2}), mean (SD)	16.55 (1.59)	17.27 (3.07)
eGFR (mL min^{-1} 1.73 m^{-2}), mean (SD)	120.91 (18.37)	127.91 (29.21)
Body surface area (m^2), mean (SD)	0.472 (0.070)	0.814 (0.254)
VTE subtype (qualifying event), *n* (%)*		
Pulmonary embolism	0	1 (11)
Vena cava thrombosis	1 (17)	2 (22)
Upper extremity thrombosis	2 (33)	3 (33)
Lower extremity thrombosis	2 (33)	1 (11)
Sinus venous thrombosis	0	5 (56)
Central venous line-related thrombosis	2 (33)	2 (22)
Not specified/recorded	2 (33)	0
Anticoagulant used prior to study drug, *n* (%)*		
UFH	1 (17)	1 (11)
LMWH	2 (33)	7 (78)
VKA	0	3 (33)
Data not available	4 (67)	1 (11)

BMI, body mass index; eGFR, estimated glomerular filtration rate; LMWH, low molecular weight heparin; SD, standard deviation; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism. All demographic information was recorded at visit 1 (screening), except for age (years), which was based on the time of the study drug intake. *Patients could have more than one type of VTE or be receiving more than one anticoagulant prior to the study drug.

parameter estimates were not significantly different from zero. Age did not appear to affect the PK–PD relationship when analyzed by linear regression with age as a covariate.

Preliminary safety results

AEs during screening were reported in three patients (17%), all in the single-dose groups: one patient in the group aged 1 to < 2 years had mild respiratory tract infection, one patient aged 2 years had nasopharyngitis and ear pain, both of which were mild in intensity, and one patient aged 7 years had mild back pain. All three patients recovered. One patient (6%) aged 6 years in the multiple-dose group experienced leukopenia and dizziness during the on-treatment period. The patient recovered from both of these AEs, which were mild and considered to be unrelated to the study drug.

Table 3 Total dabigatran plasma concentration in single-dose groups

	Planned time after dosing (h)						C_{max} (ng mL^{-1})	t_{max} (h)*	AUC_{0-tz} (ng mL^{-1} h^{-1})
	1	2	4	6	10				
Single dose, 1 to < 2 years									
N	4	6	6	6	6		6	6	6
gMean (ng mL^{-1})	79.4	129	91.0	62.9	34.8		129	1.99	715
gCV (%)	45.6	9.84	23.0	32.6	41.4		9.84	(1.92–2.20)	22.5
Median, (IQR)	82.2 (56.1–114)	133 (126–138)	85.0 (76.8–99.8)	53.7 (49.8–83.1)	30.2 (26.1–56.1)		133 (126–138)	1.99 (1.98–2.05)	642 (603–894)
Single dose, 2 to < 12 years									
N	9	9	9	9	9		9	9	9
gMean (ng mL^{-1})	90.6	114.0	87.7	56.2	28.2		116	2.00	658
gCV (%)	48.8	37.9	31.6	34.2	37.0		38.6	(1.03–4.02)	32.5
Median (IQR)	78.0 (75.6–124)	133 (98.2–140)	86.0 (76.5–109)	55.9 (44.9–66.0)	28.8 (23.0–33.9)		136 (98.2–140)	2.00 (2.00–2.03)	692 (597–821)

AUC_{0-tz}, area under the concentration–time curve from time interval 0 up to the last quantifiable data point; C_{max}, maximum concentration; gCV, geometric coefficient of variation; gMean, geometric mean; IQR, interquartile range; t_{max}, time from dosing to maximum concentration. *Median and range (minimum–maximum) are given for t_{max} rather than gMean and gCV.

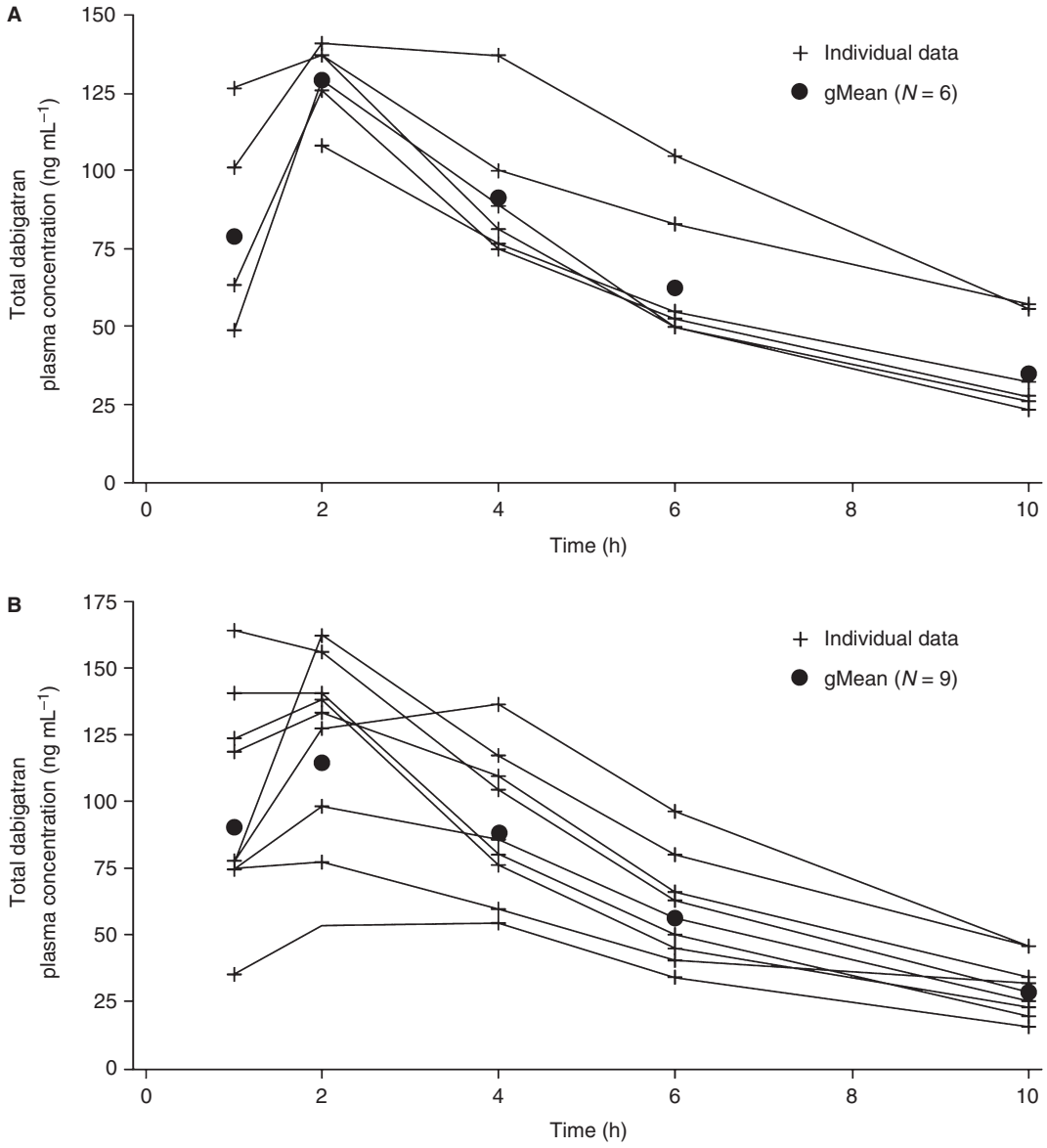

Fig. 2. Total dabigatran plasma concentration in single-dose groups. Total dabigatran plasma concentration for (A) single-dose patients aged 1 to < 2 years and (B) single-dose patients aged 2 to < 12 years. gMean, geometric mean.

No AEs occurred during the post-treatment or post-study periods, and there were no deaths, AEs leading to discontinuation, or serious, severe or drug-related AEs. There were no reports of bleeding events, recurrent VTE or post-thrombotic syndrome, and there were no clinically significant findings from laboratory analyses as compared with baseline.

Tolerability was 'good' in six patients (33%), 'satisfactory' in three (17%), 'not satisfactory' in six (33%), 'bad' in two (11%), and not assessable in one (6%). Taste, which was assessed only in the age groups aged 2 to < 12 years, was reported as 'satisfactory' by five patients (28%), 'bad' by two (11%), and 'very bad' by three (17%); no patient reported taste as 'good' or 'very good'. Data were missing for eight patients (44%). In addition, taste was described as 'bitter' by five patients (28%) and 'sour' by four (22%); no patients considered taste to be 'sweet or salty', one patient (6%) selected none of the above, and data were missing for eight patients (44%).

Discussion

The current study assessed the pharmacokinetics, pharmacodynamics, safety, and tolerability of the DE OLF in pediatric patients aged 1 to < 12 years, which is necessary to determine whether the results reflect those observed in the adult population. Projected steady-state dabigatran trough concentrations in the current study were largely comparable to those seen in adults with VTE. Projections were necessary, as steady-state concentrations (in adults)

Table 4 Projected steady-state total dabigatran trough concentrations in patients aged 1 to < 2 years and patients aged 2 to < 12 years as compared with total dabigatran trough concentrations in adults in RE-COVER

	Current study in pediatric patients (single-dose groups only)				RE-COVER (adults)*
	Total dabigatran concentration 10 h postdose (ng mL^{-1})		Projected steady-state total dabigatran trough concentration (ng mL^{-1})		
	1 to < 2 years	2 to < 12 years	1 to < 2 years	2 to < 12 years	Total dabigatran trough concentration (ng mL^{-1})
N	6	9	6	9	850
gMean	34.8(a)	28.2(b)	53.1–87.6(c)	40.8–67.3(d)	59.7
gCV (%)	41.4	37.0	–	–	81.6
Median	30.2	28.8	–	–	58.7
CV (%)	41.7	35.4	–	–	79.7
Q1	–	–	–	–	38.6
Q3	–	–	–	–	94.5
P10					26.3
P90					146

CV, coefficient of variation; gCV, geometric coefficient of variation; gMean, geometric mean; P10, 10th percentile; P90, 90th percentile; Q1, first quartile; Q3, third quartile. Projected steady-state trough (d) or (c) = (C10 [b] or [a])/BA factor × AR × 2-h decay rate. BA is bioavailability (dose conversion) factor (0.646), and AR is accumulation ratio, i.e. $1/(1 - e^{-k\tau})$, where $k = 0.693/t_{1/2}$, $\tau = 12$ h, and $t_{1/2} = 5$–10 h. The 2-h decay rate = e^{-kt}; where $k = t_{1/2}/0.693$, $t = 2$ h, and $t_{1/2} = 5$–10 h. *At day 30.

Table 5 Pharmacodynamic results for a single dose, for patients aged 1 to < 2 years and 2 to < 12 years

	APTT			dTT			ECT		
	N	Mean	CV (%)	*N*	Mean	CV (%)	*N*	Mean	CV (%)
Single-dose patients aged 1 to < 2 years									
E_{base} (s)	6	32.3	24.6	6	31.9	4.67	6	36.9	7.49
E_2 (s)	6	47.5	24.7	6	46.6	6.02	6	79.8	5.15
E_{10} (s)	5	40.3	19.6	6	35.5	6.02	5	49.7	5.36
ER_2 (ratio)	6	1.51	20.5	6	1.46	4.27	6	2.17	11
ER_{10} (ratio)	5	1.27	12.5	6	1.11	4.1	5	1.33	7.56
Single-dose patients aged 2 to < 12 years									
E_{base} (s)	7	34.9	24.5	9	35.6	10.1	6	36.8	10.5
E_2 (s)	9	77	54.6	9	53.6	18.4	7	73.6	22.1
E_{10} (s)	8	58.4	40.6	9	39.7	9.76	7	52.2	10.3
ER_2 (ratio)	7	2.48	53.1	9	1.51	18.5	5	2.04	32.6
ER_{10} (ratio)	6	2.1	59.4	9	1.12	9.43	5	1.44	14.1

APTT, activated partial thromboplastin time; CV, coefficient of variation; dTT, dilute thrombin time; E_2, effect 2 h postdose; E_{10}, effect at 10 h postdose; E_{base}, baseline effect; ECT, ecarin clotting time.

cannot be compared with single-dose conditions. To project the steady-state dabigatran plasma concentration, gMean concentrations at 10 h after dosing were extrapolated by use of an accumulation ratio based on $t_{1/2}$ and the dosing interval (for a twice-daily dosing regimen). As plasma samples were only collected up to 10 h postdose, an exact estimation of the true $t_{1/2}$ of dabigatran in children was not possible (a sampling time of 48 h is typically required for a reliable estimation of dabigatran half-life, which was not feasible in this pediatric population). On the basis of the plasma samples taken at 10 h postdose and data from younger adults, the $t_{1/2}$ of dabigatran in pediatric patients was assumed to be 5–10 h; estimation of the $t_{1/2}$ is a potential limitation associated with the projections.

In the current study, a dose conversion factor was used to correct for dosing with the OLF based on results from a relative bioavailability study (NCT02171611). However, the findings from a larger relative bioavailability trial (NCT02044367) using multiple doses subsequently showed a much smaller difference in exposure between the two formulations, so a conversion factor was not necessary. If no conversion factor had been applied in the current study, the gMean C_{10} value of total dabigatran would have been higher in both pediatric age groups (the gMean C_{10} value shown in Table 3 was divided by 0.646 before extrapolation to the steady-state trough concentration, as described in the footnote of Table 4). No conversion factor will be applied to dosing nomograms in future pediatric studies.

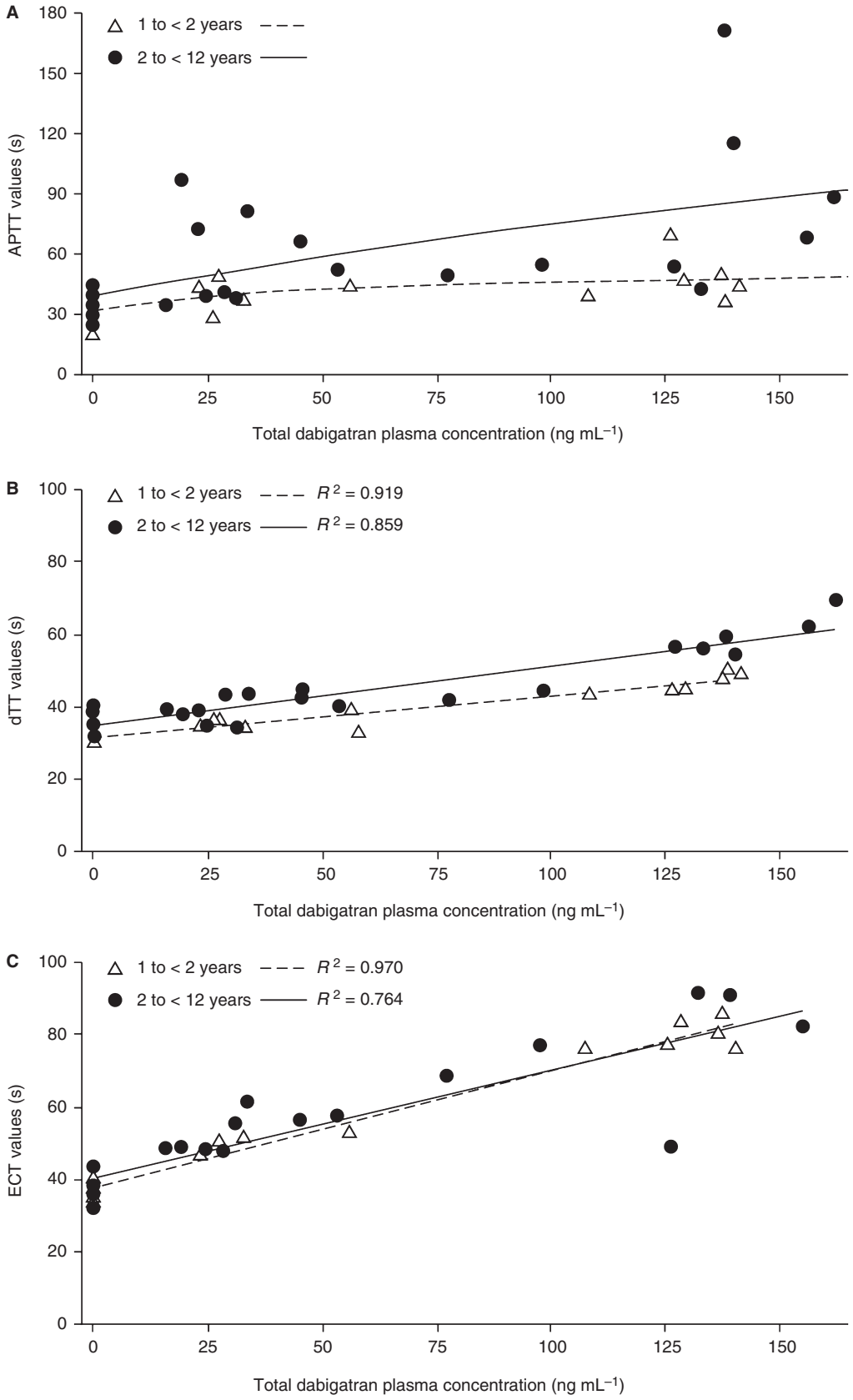

Fig. 3. PK-PD relationships. Relationships between total dabigatran plasma concentration and (A) activated partial thromboplastin time (APTT) (B) dilute thrombin time (dTT) and (C) ecarin clotting time (ECT) in patients aged 1 to < 2 years and 2 to < 12 years. In (A), samples from two patients at – 2 h (pre-dose) and two patients at 10 h were excluded, and in (C) samples from one patient at – 2 h (predose) and two patients at 10 h were excluded.

The results of the current study show that there was a linear PK–PD relationship for dTT and ECT, similar to that seen in adults and adolescents with VTE. The PK–PD relationship for APTT was non-linear, as observed in the adult population.

The results of the taste assessment were mixed, with 11% and 17% of patients rating the taste as 'bad' or 'very bad', respectively. However, the tolerability and preliminary safety profiles were otherwise favorable. In addition to the OLF, a pellet formulation of DE is under development, and this will also be subject to acceptability and taste assessments. Currently, no specific pediatric formulations of antithrombotic drugs are available, but they are under development. Therefore, a palatable pediatric formulation such as the OLF or a pellet formulation would provide a much needed alternative for children who have difficulties with injections or swallowing capsules.

The study has certain limitations, including the reliance on projected steady-state dabigatran concentrations. Another limitation is the population size, which is small relative to the broad age range of the eligible population from a safety perspective. However, for a PK analysis, which is the focus of the study, the sample size was considered to be sufficient. There was a lack of evaluable data from the multiple-dose group (only three patients). In addition, the three patients in the multiple-dose group were dosed according to a weight-based nomogram, which was replaced with an age-based and weight-based nomogram in the single-dose groups and in subsequent pediatric studies. Given the limited study power, the safety confidence limits are too wide to conclude that dabigatran is safe in children. Indeed, the safety and efficacy of DE in pediatric patients are currently being evaluated in additional clinical studies.

In summary, the results of the current study support further evaluation of DE in pediatric patients with VTE, and provide support for the dosing regimen in the ongoing phase IIb/III studies. DE may provide a new treatment option in this patient population, overcoming the limitations associated with current treatments.

Addendum

J. M. L. Halton was the coordinating investigator of the trial, and was involved in concept design, analysis, interpretation of data, writing and reviewing the draft manuscript, and approval of the final version to be published. M. Albisetti is a member of a Pediatric Expert Working Group for Boehringer Ingelheim. B. Biss Trial Clinical Monitor. L. Bomgaars is a member of a Pediatric Expert Working Group for Boehringer Ingelheim. M. Brueckmann contributed to the trial design, study protocol, and trial conduct. S. Gropper contributed to the trial design, study protocol, and trial conduct. R. Harper contributed to the trial design, study protocol, and trial conduct. F. Huang contributed to the trial design, study protocol, data analysis, and study report writing. M. Luciani is a member of a Pediatric Expert Working Group for Boehringer Ingelheim. H. Maas contributed to the trial design and study protocol. I. Tartakovsky contributed to the trial design, study protocol, and trial conduct. L. G. Mitchell was the coordinating investigator of the trial. All authors provided input and critical review of the manuscript, and approved the final manuscript.

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Disclosure of Conflict of Interests

J. M. L. Halton, M. Albisetti, M. Luciani, and L. Bomgaars are members of a Pediatric Expert Working Group for Boehringer Ingelheim. B. Biss, M. Brueckmann, S. Gropper, R. Harper, F. Huang, H. Maas, and I. Tartakovsky are employees of Boehringer Ingelheim. L. G. Mitchell is a consultant for Boehringer Ingelheim, Pfizer, and Bristol-Myers Squibb.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Assessments made during the study.
Table S2. Baseline characteristics of patients in the multiple-dose group.
Table S3. Free dabigatran plasma concentrations in single-dose groups.
Table S4. Total dabigatran concentration in the multiple-dose group in patients aged 2 to < 12 years (too few evaluable assessments for summary statistics).

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